

# Physiotherapy Versus Calcitonin Spray-Added Physiotherapy for Treatment of Complex Regional Pain Syndrome

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Received 2016 November 05; Revised 2017 February 07; Accepted 2017 March 01.

## Abstract

**Background:** Complex regional pain syndrome (CRPS) is a common complication in orthopedic surgeries. The present study aimed at evaluating the effect of calcitonin in the treatment of patients with CRPS.

**Methods:** In this clinical trial study, 30 CRPS patients were randomly divided into 2 groups: 16 patients were only treated with physiotherapy and 14 with physiotherapy and calcitonin spray. They were matched according to age, sex, and type of fractures. Changes in range of motion, swelling, and pain were compared between the 2 groups after the fourth month.

**Results:** No significant difference was obtained between the 2 groups in motion range amelioration and swelling decrease. However, the patients in physiotherapy and calcitonin group had less pain than the control group. No significant difference was found between the 2 groups in pain after the first and second months of treatment. However, patients' pain showed a significant difference at the end of the third and fourth months ( $44.3 \pm 10.5$  vs.  $56.7 \pm 13.8$ ) ( $P = 0.01$ ). There was no side effect in calcitonin group.

**Conclusions:** The use of calcitonin spray with physical therapy efficiently reduced CRPS patients' pain. It also reduced the need for analgesic consumption. However, it did not affect the functional outcome.

**Keywords:** Complex Regional Pain Syndrome, Calcitonin, Physiotherapy

## 1. Background

Complex regional pain syndrome (CRPS) usually develops after trauma, surgeries, or vascular events including heart or cerebral stroke. Diagnostic criteria of this syndrome are as follow: pain; swelling; range of motion limitations of joints (passive and active); vasomotor disorder, such as regulation blood circulation; cutaneous changes including its color changing; reduction of bones density; temperature variations; and muscles atrophy. Exact pathogenesis of the syndrome is not known (1, 2). Evidence exists on the effects of sympathetic system on its incidence (3). Psychological factors have also been considered in pathogenesis of complex regional pain syndrome. For example, the syndrome is more observed among the patients with transformation and artificial disorders (3). Suggested mechanisms of pain include release of inflammatory mediators, such as Y neuropeptide, P substance, 6 - 8 interleukin, interleukin - $\beta$ , TNF, and calcitonin gene related peptide. Complex regional pain syndrome is of the following 2 types: Type I, where there is not any known neural damage in 90% of the cases; Type II, where there is known neural damage in 10% of the cases, which was previously known as Causalgia (4).

Pain relief interventions include a range of nonsteroid anti-inflammatory medicines to sympathetic blocks and interspinal injection (5). Calcitonin is a polypeptide hormone secreted by parafollicular cells of thyroid gland, which initially acts on bones. Also, it affects kidney and digestion system and controls absorption process of bone tissue manifested through reduction of its osteoclast and activity (6-9). The present study was an attempt to evaluate the effects of calcitonin on complex regional pain syndrome I (10). On the other hand, calcitonin gene-related peptide (CGRP) is a neuropeptide produced by alternative splicing of the calcitonin gene, e.g., in primary afferent neurons. CGRP is involved in the generation of pain and hyperalgesia (10). The present study aimed at evaluating the effects of calcitonin nasal spray in combination with physiotherapy for treating complex regional pain syndrome (CRPS).

## 2. Methods

This was a clinical trial study and the population under study consisted of the patients, who had undergone surgery in Tabriz Shohada hospital through 6 years (from

2007 to 2013) and showed complex regional pain syndrome symptoms during their treatment process. The diagnostic entity of CRPS (published in the international association for the study of pain's taxonomy monograph in 1994; international association for the study of pain (IASP)) was used. Inclusion criteria were as follow: patients, who had distal radius fractures treated surgically and had a wrist pain; allodynia; dysesthesias; hyperpathia; vascular instability; skin temperature; color and swelling; and texture changes with subsequent immobility.

The exclusion criteria were as follow: involvement of peripheral nerves; presence of muscles degenerating trauma; presence of joint degeneration; previous severe joint arthritis; and presence of mental disorders and other metabolic disorder (diabetes and etc.). The patients were simply and randomly divided into 2 groups based on the number of registered cases: group I was treated with physiotherapy and group II underwent physiotherapy in association with spray calcitonin consumption as one puff per day (equal to 200 IN) (6). Physiotherapy protocol was the same for all patients and included returning motor domain of the limbs, inactivating points that served as trigger points, sensitizing, and training motions to return their motor domain and strengthen the muscles. Patients were examined every month and their pain, swelling, and range of wrist movements were recorded. Written informed consent was obtained from all the patients. Ethics committee of Tabriz University of Medical Sciences approved the study.

### 2.1. Patients

During the study, 760 patients underwent orthopedic surgeries for traumatic distal radius fractures; of them, 37 patients (4.8%) suffered from symptoms of complex regional pain syndrome despite early commence of the motions. In this study, degeneration of joint surface, psychologist-confirmed hysteric mental disorders, and extended defect, and muscle necrosis led to exclusion of 7 cases from the study. The remaining 30 patients were divided into 2 groups consisting of 14 and 16 patients. The 16-member group was treated only using physiotherapy and the other group was treated using physiotherapy and calcitonin spray.

At initial stages of the study, patients' palliative medicine dosage was determined to evaluate their pain. Additionally, domain of joint motion in the affected organ was specified in angle. Considering that there are a variety of involved joints mostly due to their closeness to the damage and fracture area, motion domain of every joint was measured and compared with the intact one. Improvement of motion domain at every examination was compared with the condition at the treatment

onset, and the results were stated in percent. Inflammation rate was determined through measuring circumference of the affected organ and its comparison with the healthy organ in millimeter. At the beginning of the study, amount of the medicine consumption, limitation of motion domains, and edema of the organs were regarded as 100%. Then, every patient was periodically examined every month and followed-up for 4 months. In addition to determining edema and motion domain of the affected joint, the patients' pain was measured and registered based on consumption of palliative medicines, including acetaminophen, ibuprofen, opioid, and changing of the drug dosage. Pain relief rate, reduction of the consumed medicine dosage, and edema were specified as reduction percentage in comparison with the initial stage of the study. Also, increasing motion domain was stated as increase percentage. The results obtained from the 2 groups were compared. Pain severity was determined based on VAS (visual analogue score) method, ranging from zero (painless) to 100 (the most severe pain). Swelling was calculated based on the clinical picture and the image J software. Wrist range of motion was determined based on clinical examination goniometer. Wrist power and grip were measured at the end of the fourth month between the 2 groups. Additionally, the hand functional outcome (secondary outcome) was evaluated using Disability of arm, shoulder, and hand (DASH) scoring at the end of the fourth month.

### 2.2. Statistical Analysis

Statistical analyses were done using the SPSS software (statistical package for the social sciences, Version 16.0, SPSS Inc; Chicago, Ill, USA). Continuous variables were shown as mean  $\pm$  standard deviation. Normality of the distributions was checked for each variable using the Kolmogorov-Smirnov test. Chi square statistical test was used to study qualitative variables. Independent t test and Mann-Whitney test were used to compare the variation percentage of edema change and compare median (VAS), respectively. Repeated measure test was used to evaluate variable changes in the follow-up. Significance level was set at  $P \leq 0.05$ .

## 3. Results

A total of 16 patients in the physiotherapy group, with the mean age of  $38 \pm 12$  years including 3 females (18.7%) and 13 males (81.3%), were compared with 14 patients in the physiotherapy + calcitonin group, with the mean age of  $36 \pm 9$  years including 4 females (28.6%) and 10 males (71.4%). No significant difference was found between the 2 groups in sex and age. The comparison between the 2

groups at the end of the fourth month is listed in Table 1. In case of patients' functional outcome according to DASH score and ROM, no difference was observed 4 months after treatment. The results considering motion domain demonstrated that no significant difference in the follow-up time between the 2 groups ( $P = 0.8$ ) (Figure 1).

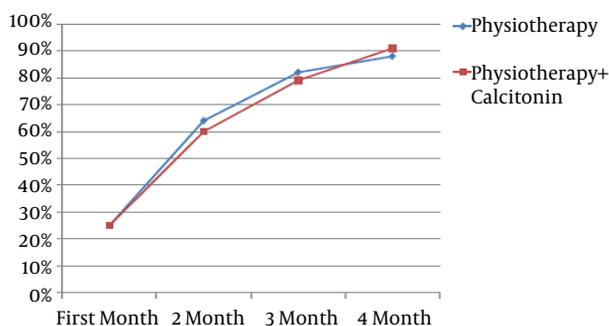


Figure 1. Percent Range of Motion Improvement in Joint over Time

Results on the variation rate of inflammation (Figure 2) revealed that reduction of inflammation was not different in 4 month follow-up in the 2 groups.

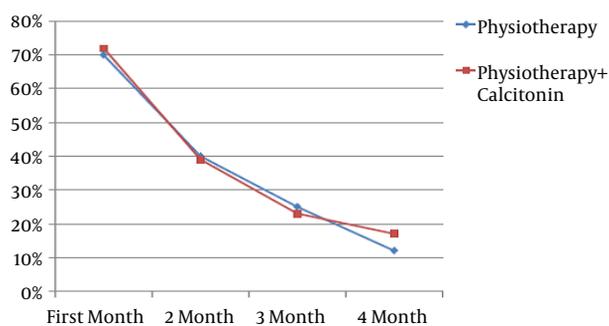


Figure 2. Percent of Swelling Reduction in Joints Over Time

Consumption rate of analgesic medications was 75% in the physiotherapy and 72% in the physiotherapy + spray calcitonin group during the first month compared to the beginning of the study ( $P = 0.68$ ). Analgesic consumption was 22% and 8% in the physiotherapy and physiotherapy + spray calcitonin group, respectively, during the fourth month, so a significant difference was observed ( $P = 0.016$ ) (Figure 3). The resulted outcomes demonstrate that the mean of pain severity based on VAS scale was not significantly different at the end of the first and second months in the 2 groups. However, there was a significant difference at the end of the third and fourth months (Table 2).

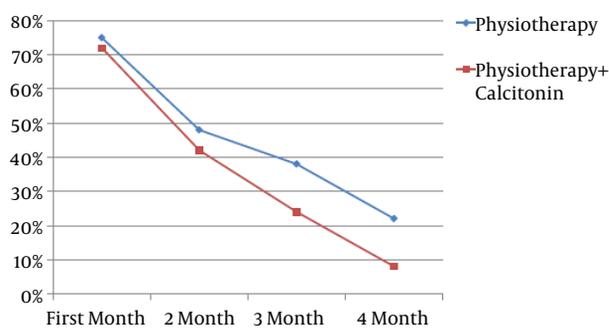


Figure 3. Percent of Analgesic Dose Reduction over Time

#### 4. Discussion

The present study concluded that adding spray calcitonin to routine mentioned treatment method dose not lead to improvement of motion limitation or decrease of inflammation. Rather, it relieves the patients' pain and analgesic consumption level during a 4-month follow-up period. Considering previous studies using bone scan, bone vascular parameters improved after using calcitonin as a treatment method. Nonetheless, clinical recovery was realized by several months delay (11). There are few studies regarding the effects of spray calcitonin in treating complex regional pain syndrome. Using calcitonin spray in treating patients' pain associated with peripheral nervous system involvement is considered. The calcitonin mechanism of action in peripheral nerve system has not been fully determined (12). In addition to its hypocalcemic effect, there are several proposed hypotheses ranging from peripheral to central nociception mechanisms including serotonergic or catecholaminergic effect, inhibiting synthesis of the inflammatory mediators, and provoking the releasing of the endogenous opioid neuropeptides, such as endorphins. In the latest findings, it was revealed that intranasal calcitonin spray may mitigate pain intensity, increase shoulder ROM, and improve functional outcome in patients suffering from shoulder adhesive capsulitis (13). For the first time, Kissling et al. studied the effects of calcitonin in preventing the repetition of the complex regional pain syndrome in patients who previously experienced it. The study referred to recurrence of the syndrome only in one patient (11).

Previous studies suggested a palliative state similar to opioid for calcitonin, which may be a distorting factor in our study (14). Tran et al. s' review of the evidences derived from randomized controlled trials pertaining to the treatment of complex regional pain syndrome (CRPS) showed that the use of calcitonin, vasodilators, or sympatholytic and neuromodulative intravenous regional blockade have

**Table 1.** Comparison of Pain Intensity before Treatment and Final Outcome of Patients Between the 2 Groups

Variable	Calcitonin with Physiotherapy Group (N = 16)	Physiotherapy Group (N = 14)	P Value
Pain intensity: VAS (mean $\pm$ SD) in pre treatment	89.6 $\pm$ 9.7	88.4 $\pm$ 10.2	0.2
DASH, mean $\pm$ SD	42.4 $\pm$ 5.8	41.4 $\pm$ 5.2	0.1
Hand grip, mean $\pm$ SD, kg	11.5 $\pm$ 2.4	10.2 $\pm$ 8.5	0.3
Hand pinch, mean $\pm$ SD, kg	9.4 $\pm$ 6.1	10.2 $\pm$ 4.1	0.1
ROM in flexion, %	20.7 $\pm$ 18.6	22.3 $\pm$ 16.5	0.8
ROM in extension, %	19.3 $\pm$ 15.4	16.8 $\pm$ 14.3	0.4
ROM in supination, %	13.7 $\pm$ 12.4	14.5 $\pm$ 12.2	0.1
ROM in pronation, %	16.8 $\pm$ 11.3	17.3 $\pm$ 14.7	0.3

**Table 2.** Monthly Comparison of Pain Intensity Between the 2 Groups with CRPS

Variable	Calcitonin with Physiotherapy Group (N = 16)	Physiotherapy Group (N = 14)	P Value
First month VAS score	78.8 $\pm$ 21.1	81.3 $\pm$ 11.3	0.1
Second month VAS score	59.4 $\pm$ 1.6	61.8 $\pm$ 10.6	0.2
Third month VAS score	45 $\pm$ 22.4	58.3 $\pm$ 14.6	0.02 <sup>a</sup>
Fourth month VAS score	44.3 $\pm$ 10.5	56.7 $\pm$ 13.8	0.01 <sup>a</sup>

<sup>a</sup>Significant difference.

no effects on patient pain and functional outcome (15). Ruegg S suggested that calcitonin and the biphosphonates inhibit osteoclasts and cause loss of bone mass and may reduce pain in CRPS (16). According to our findings, calcitonin had a positive effect on patients' pain, but their functional outcome was not affected. During the study, no complication associated with consumption of calcitonin was observed. It is recommended that calcitonin be used in treating complex regional pain syndrome considering its coverage by the insurance companies as well as its easy application.

#### 4.1. Limitation of the Study

In this study, we tried to match the 2 groups as much as possible. Nevertheless, the difference in patients' activity and pain threshold was different and there was no real possibility of synchronization, so it might have affected our results.

#### 4.2. Conclusions

According to our findings, the use of calcitonin spray can only affect the pain of patients with CRPS. It did not affect the patients' outcome and functional abilities. It seems that calcitonin spray can be used to control pain in patients suffering from CRPS.

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